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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/634,145	08/04/2003	Chew Kiat Heng	NAA 0018 PA/41049.20	5097

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EXAMINER	
WHALEY, PABLO S	
ART UNIT	**PAPER NUMBER**
1631	
MAIL DATE	**DELIVERY MODE**
02/13/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/634,145	HENG ET AL.	
	Examiner	Art Unit	
	PABLO WHALEY	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 November 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15 and 17-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15 and 17-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

Claims 1-15 and 17-30 are pending.

Claims 1-15 and 17-30 are rejected.

Claim 16 is cancelled.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-11, 18-23, 28, 29, and 30 are rejected under 35 U.S.C. 103(a) as being made obvious by Tibshirani (Statistics In Medicine, 1997, Vol. 16, p.385-395), in view of Nguyen et al. (Bioinformatics, 2002, Vol. 18, No. 12, p.1625-1632), in view of Mariani et al. (Breast Cancer Research and Treatment, 1997, Vol. 44, p. 167–178), and in view of Walters (What is a Cox Model, Copyright 2001, Vol. 1, No. 10, p.1-8)

Tibshirani teaches a computer-implemented method for determining variables for a Cox proportional-hazard model [Abstract]. In particular, Tibshirani teaches collecting a plurality of data sets

associated with cancer comprising Karnofsky scores, age, sex, state of disease, cell type, treatment, etc. [p.387-389], which shows 'indicators of disease status', and 'non-genetic' data. Tibshirani teaches a general Cox statistical model for calculating risk [Section 1, Equations 1 and 2] using non-genetic data [p.387, Example 3], wherein the program is stored on a computer [p.386, Section 2]. Tibshirani teaches optimizing model parameters by calculating deviations in data sets using seventeen variables and using full, stepwise, and Lasso models (i.e. which incorporate minimized weighted values as described in Section 2) for data simulations [p.390, Table I, p.391, Section 5.2, and Fig. 2]. Tibshirani teaches optimization of model parameters via an argmin function (i.e. target function) [p.386, ¶ 1]. Tibshirani teaches grouping of data indicative of a plurality of factors, wherein groups include values of 0 and 1, determining scores for each variable [Table I], and discarding missing values of data [p.389, ¶ 1]. Tibshirani teaches the comparison of models after simulation to select and output an optimum model with optimum parameters, wherein one model uses a different number of parameters [Table I], and shows selecting the appropriate number of coefficients [Table 1,and p.391, Section 5.1].

Tibshirani does not teach collecting genetic data, as in claims 1, 21, and 28.

Tibshirani does not specifically teach indicating a statistical significance associated with calculated weighted deviates, as in claims 1, 21, and 28.

Tibshirani does not specifically teach calculating weights determined with a constraint that weights associated with sets of data having like genetic data are the same, as in claims 1, 2, 3, 19, 20, 21, and 28-30.

Nguyen teaches a hazard regression models using gene expression data for predicting cancer survival [Abstract, p.1626, Methods]. In particular, Nguyen teaches optimizing model parameters by fitting data [p.1626, Col. 2, ¶3, p.1630, Col. 1, ¶2, ¶3, and Fig. 1], as in claims 1, 21, and 28. Furthermore, Nguyen teaches calculating weights that are associated with genetic data and subjected to a constraint that the weights all are equivalent with respect to orthogonality, as in claims 1, 21, and 28, which shows

weights associated with genetic data are the same. This method is beneficial in that it enables scientists to improve the prediction of cancer survival probabilities using high-dimension data [p.1630, Discussion].

Mariani teaches the analysis of non-genetic data using Cox hazard models and neural network models [Abstract and p.175-176, Appendix]. Mariani also teaches hazard equations for describing coefficients as a linear combination of weights [Col. 175, Col. 2 and p.176, Col. 1] and optimization of weights based on differences between observed and predicted values [p.176, Col. 1, ¶1]. Mariani also suggests a need for flexible models that allow for the integration of different types of predictive factors, especially in the case of low predictiveness [p.175, Col.1].

Walters teaches a Cox regression model for describing a relationship between a plurality of different types of data, equations for calculating the predicted risk (i.e. weighted deviates) based upon a sum of weights [p.4, Col. 1 and Table 2], and determining the statistical significance of each of the variables [p. 4, Col. 2, last ¶], as in claims 1, 21, and 28.

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the statistical model of Tibshirani by additionally collecting genetic data for analysis, as in claims 1, 21, and 28, since Nguyen teaches collecting genetic data for hazard regression analysis [Abstract, p.1626, Methods]. The motivation would have been to develop a more robust predicted risk model that accounts for genetic risk components and multiple predictive factors, as suggested by Mariani [p.173, Col. 1, ¶3, p.175, Col. 1].

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the statistical model of Tibshirani by indicating a statistical significance associated with calculated weighted deviates, as in claims 1, 21, and 28, since Walters calculates the predicted risk (i.e. weighted deviates) based upon a sum of weights [p.4, Col. 1 and Table 2], and determines the statistical significance of each of the variables [p. 4, Col. 2, last ¶], as in claims 1, 21, and 28. The

motivation would have been to give the proportional changes that can be expected in the hazard, as suggested by Walters [p.4, Col. 2].

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the statistical model of Tibshirani by calculating weights determined with a constraint that weights associated with sets of data having like genetic data are the same, as in claims 1, 2, 3, 19, 20, 21, and 28-30, since Nguyen teaches calculating weights that are associated with a linear combination of genes (i.e. like genetic data) and are subjected to the constraint that the weights are equivalent with respect to orthogonality, which shows weights associated with genetic data that are the same, and since Tibshirani shows minimizing weights subject to a constrain [p.386]. The motivation would have been to improve model response by using an optimized linear combination of predictors and weights, as suggested by Nguyen [p.1626, Col. 2, last ¶].

Claims 1-15 and 17- 30 are rejected under 35 U.S.C. 103(a) as being made obvious by Tibshirani (Statistics In Medicine, 1997, Vol. 16, p.385-395), in view of Nguyen et al. (Bioinformatics, 2002, Vol. 18, No. 12, p.1625-1632), in view of Mariani et al. (Breast Cancer Research and Treatment, 1997, Vol. 44, p. 167–178), and in view of Walters (What is a Cox Model, Copyright 2001, Vol. 1, No. 10, p.1-8), as applied to claims 1-11, 18-23, 28, 29, and 30 above, and further in view of Lazzeroni et al. (Proceedings of the Survey Research Methods, 1990, p. 260-265).

Tibshirani, Nguyen, Mariani, and Walters make obvious a computer-implemented for predicting disease risk using genetic and non-genetic data, as set forth above.

Tibshirani, Nguyen, Mariani, and Walters do not specifically teach imputing missing data, as in claim 12, or calculating adjustment factors, as in claims 13, 14, and 27.

Lazzeroni teaches methods for determining the robustness of models using imputation techniques. In particular, Lazzeroni teach imputing missing data based on regression models [Sections 1 and 2], as in claim 12. In addition, Lazzeroni teaches weights that are weighted by adjustment factors that have been calculated in order to correct for possible bias in the population data [p.261, Col. 2, ¶3, and p. 262, Col. 1, ¶1], as in claims 13, 14, and 27. Lazzeroni does not teach the particular equation for calculating adjustment factors based on a ratio between population members, as in claims 14 and 27. However, this limitation would have been obvious to one of ordinary skill in the art since Lazzeroni teaches adjustment factors based on a difference between population members.

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention practice the method made obvious by Tibshirani, Nguyen, and Mariani in combination with the analysis methods for imputing missing data and calculating adjustment factors, as taught by Lazzeroni, since Lazzeroni teaches methods for assessing the robustness of linear regression models that use population data [Section 1]. One of ordinary skill in the art would have been motivated to combine the teachings of Lazzeroni in order to improve model accuracy by accounting for model misspecification and possible bias in the predictive data, as suggested by Lazzeroni [p.262, Col. 1, ¶1].

Claims 1-11, 18-26, and 28-30 are rejected under 35 U.S.C. 103(a) as being made obvious by Tibshirani (Statistics In Medicine, 1997, Vol. 16, p.385-395), in view of Nguyen et al. (Bioinformatics, 2002, Vol. 18, No. 12, p.1625-1632), in view of Mariani et al. (Breast Cancer Research and Treatment, 1997, Vol. 44, p. 167–178), and in view of Walters (What is a Cox Model, Copyright 2001, Vol. 1, No. 10, p.1-8), as applied to claims 1-11, 18-23, and 28-30 above, and further in view of Nelson et al. (Journal of Clinical Epidemiology, 1998, Vol. 51, No. 3, pp. 199–209).

Tibshirani, Nguyen, Mariani, and Walters make obvious a computer-implemented for predicting disease risk using genetic and non-genetic data, as set forth above.

Tibshirani, Nguyen, Mariani, and Walters do not specifically teach recursively dividing data, as in claims 24-26.

Nelson teaches a method of partitioning data to determine disease subgroups [Abstract and Fig. 1]. In particular, Nelson teaches the recursive partitioning of data, wherein subjects are assigned to subsets according to a set of predictor variables [Abstract and Fig. 1], and splitting criteria (i.e. Gini indexing) for identifying variables that minimize variance between case (i.e. disease) and control groups (i.e. reference) [p.207 and 208, Appendix A, and Fig. 1], as in claims 24-26. Nelson suggests their method may uncover interactions between predictive variables that may be overlooked in traditional case-control studies [Abstract].

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention practice the method made obvious by Tibshirani, Nguyen, and Mariani using recursive partitioning as taught by Nelson et al., since Nelson suggests that recursive partitioning is commonly used for disease prediction [p.201, Col. 1, ¶ 1] and since all teach methods of regression analysis [p.204, Col. 1, ¶ 2]. One of ordinary skill in the art would have been motivated to further analyze the risk variables using the method of Nelson in order to improve model accuracy by accounting for overlooked interactions between predictive variables, as suggested by Nelson [Abstract and p.208, Col. 1, ¶2].

Response to Arguments

Applicants' arguments, filed 11/10/2008, that Tibshirani does not teach "calculating weights determined with a constraint that weights associated with sets of data having like genetic data are the same" have been fully considered. In response, Nguyen teaches a hazard regression models using gene expression data for predicting cancer survival [Abstract, p.1626, Methods]. In particular, Nguyen teaches calculating weights that are associated with genetic data and subjected to a constraint that the weights all

are equivalent with respect to orthogonality, as in claims 1, 21, and 28, which shows weights associated with genetic data are the same. Therefore, it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the statistical model of Tibshirani by calculating weights determined with a constraint that weights associated with sets of data having like genetic data are the same, as in claims 1, 2, 3, 19, 20, 21, and 28-30, since Nguyen teaches calculating weights that are associated with a linear combination of genes (i.e. like genetic data) and are subjected to the constraint that the weights are equivalent with respect to orthogonality, which shows weights associated with genetic data that are the same, and since Tibshirani shows minimizing weights subject to a constrain [p.386]. The motivation would have been to improve model response by using an optimized linear combination of predictors and weights, as suggested by Nguyen [p.1626, Col. 2, last ¶]. Therefore the rejections are maintained.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Pablo Whaley whose telephone number is (571)272-4425. The examiner can normally be reached on 9:30am - 6pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie Moran can be reached at 571-272-0720. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Pablo S. Whaley/

Patent Examiner

Art Unit 1631

/John S. Brusca/
Primary Examiner, Art Unit 1631